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Postoperative adhesions and their prevention

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INTRODUCTION

The fact that adhesions can form following abdominal surgery has been known since the beginning of surgery. Yet during the early years of surgery, adhesion formation received little attention, the focus being on infection and survival. In the seventies clinical endocrinology developed explosively, driven by the introduction of oral contraceptives and by the introduction of radioimmunoassays—a technique that permitted for the first time the assay of reproductive hormones—and reproductive medicine and infertility became a subspecialty. Simultaneously, reproductive surgery developed and the prevention of postoperative adhesion formation became important. Microsurgery was introduced (1) first as a magnification tool permitting tubal reanastomosis and developing subsequently as a principle of surgery emphasizing the prevention of desiccation and gentle tissue handling (Fig. 1). Prevention of adhesion formation was mainly based upon careful observational medicine and common sense, and most of the principles became only much later experimentally confirmed. Some mistakes, however, were also introduced such as the free peritoneal graft to cover denuded peritoneal areas, a technique shown later to be strongly adhesiogenic (2).

The history of surgery and adhesion prevention cannot be viewed separately from the development of endometriosis and endometriosis surgery because cystic ovarian endometriosis is strongly associated with adhesion formation and also because endometriosis surgery is the most frequently performed fertility surgery. Diagnosis of infertility and of endometriosis and their treatment has driven the development of diagnostic laparoscopy complemented with minor laparoscopic surgical interventions and by microsurgery.

When lightweight endoscopic cameras were introduced in the mid-eighties, endoscopic surgery developed explosively replacing microsurgery and also laparotomy not only in gynecology but also in abdominal surgery and urology. This had important consequences for fertility and endometriosis surgery and for our awareness of adhesion formation. Until the early nineties, fertility surgery with prevention of adhesion formation had remained centralized in highly specialized fertility centers (3,4). We then witnessed in parallel the increasing use and success of IVF and the development of more advanced endoscopic surgery such as deep endometriosis and bowel, pelvic floor, and oncologic surgeries. With laparoscopic reproductive surgery becoming mainstream surgery, the microsurgical focus on the prevention of adhesion formation got lost. Indeed outside reproductive surgery, adhesion formation was widely considered as an unavoidable byproduct of surgery, which could largely be prevented by good quality surgery. In retrospect, it is astonishing how fast the principles of microsurgery became by and large forgotten, with the overall belief that laparoscopic surgery was "minimal invasive" surgery and thus even better than microsurgery and that adhesion formation would rapidly become a minor problem (5,6).

With the realization that laparoscopic surgery was not the solution to prevent adhesion formation (7,8), laboratory research on and clinical interest in adhesion formation revived and new products were developed. Only in the last decade, we have become aware of the clinical importance of adhesion formation, mainly though the SCAR studies (9–11). These studies clearly demonstrated that the incidences of bowel obstruction and of reoperation due to postoperative adhesions keep increasing linearly for at least 10 years and are much higher than anticipated. In addition, the awareness of postoperative adhesions as a cause of infertility and pain grew. With the awareness of the clinical importance, we realized the associated costs, the market potential, and the necessity of randomized clinical trials for new products. "Quality of surgery" obviously being a key element in these trials, we realized that quality control of the individual surgical procedure was close to non-existent (12), and video registration was introduced as a monitoring aid for these trials. And simultaneously also came the awareness that quality of surgery might be variable—that good quality surgery cannot be considered as universal with obvious consequences for the interpretation of adhesion formation statistics.

In conclusion, postoperative adhesion formation has never received the attention it deserves as evidenced by the absence of adequate keywords to search the literature. Only very recently the clinical importance has been acknowledged (13–17), stimulating research and the foundation of a dedicated society, the PAX society, today called the Peritoneum and Surgery Society (P&S), spanning gynecology and surgery.

PATHOPHYSIOLOGY OF ADHESION FORMATION

The Mesothelial Cell and the Peritoneal Cavity

Mesothelial cells form a monolayer resting on a basal membrane and an underlying connective tissue lining the organs and the wall of the abdominal cavity, the pleura, and the pericardium. Mesothelial cells have been considered to be of mesothelial origin, but recent evidence has shown that both mesothelial cells and endothelial and hematopoietic cells are derived from a common progenitor cell originating embryologically in the splanchnic mesothelium (18). More recently mesothelial stem cells, which are able to differentiate to mesothelial cells, endothelial cells, smooth muscle cells, myofibroblasts, neuronal cells, adipocytes, chondrocytes, and osteoblasts, have been described. In culture these mesothelial cells behave as epithelial cells, expressing mainly cytokeratin, but under the influence of TGF-β, HGF, or EGF, they transform into spindle-shaped mesenchymal cells expressing mainly vimentin. The relationship between mesothelial stem cells and peritoneal repair following injury remains unclear:

Figure 1 The pioneers of microsurgery at a workshop on microsurgery held in Leuven, Belgium, in 1978. (*From left to right*) Willy Boeckx, Ivo Brosens, Robert Winston, and Victor Gomel. Courtesy of I. Brosens.

Indeed it remains debated whether these cells derive from the peritoneal fluid, from the mesothelium, from the submesothelial connective tissue, from the vascular endothelium, or from blood cells. In any case, the concept of mesothelial stem cells is bound to be important for our understanding of peritoneal repair and of adhesion formation (19–21).

The roles of mesothelial cells in maintaining normal serosal membrane integrity and function is still only partially understood. They secrete glycosaminoglycans and surfactant to allow the parietal and visceral serosa to slide over each other. They actively transport fluids, cells, and particulates across the serosal membrane. They actively modulate gas resorption as CO_2 from the pneumoperitoneum (22,23). They synthesize and secrete mediators, which play important roles in regulating inflammatory, immune, and tissue repair responses, but we do not understand yet how these mesothelial cells communicate with each other and with surrounding cells as well as what the role of progenitor cells is (24).

In the absence of ovarian activity, peritoneal fluid is scanty. During the menstrual cycle, peritoneal fluid is mainly formed as an ovarian transudate arising mainly from the developing follicle or corpus luteum. Hence peritoneal fluid contains concentrations in steroid hormones that are much higher than in plasma. Mesothelial cells are highly specialized cells regulating the transport of fluid and proteins, especially those larger than 20 kDa, between the peritoneal cavity and the blood stream. For small molecules exchange is rapid by simple diffusion, but for larger molecules transfer is much slower. Thus concentrations of blood proteins such as albumin, LH, and FSH are more than 40% lower than in plasma, whereas locally secreted macromolecules as CA125 and glycodelins accumulate in peritoneal fluid with concentrations that are much higher than in plasma (25–31). Peritoneal fluid contains high amounts of macrophages, which secrete, especially when activated, such as in endometriosis, a large variety of cytokines and growth factors. Peritoneal fluid thus is a specific microenvironment with protein and hormone concentrations that are much different from plasma (32,33).

When the mesothelial cell becomes traumatized (Fig. 3), as demonstrated for hypoxia during CO_2 pneumoperitoneum, the large flat mesothelial cell retracts, known as "bulging of cells," and the highly specialized layer of contiguous peritoneal cells is transformed into a layer of individual cells and between these cells large areas of basal membrane is directly exposed (34–39). Similar effects are believed to occur in response to all types of trauma such as desiccation, mechanical, or chemical trauma. The repair of this mesothelial cell trauma is rapid, and the peritoneal lining becomes normal again within two to three days. The consequence of this effect is largely unknown. Disruption of this highly specialized membrane is bound to affect all those substances transport of which is actively regulated by the mesothelium layer. The resorption of CO_2 from a pneumoperitoneum increases (22,23), whereas diffusion of larger molecules probably is greatly enhanced. It remains unclear to what extend this is associated with an inflammatory reaction and what the role is of attraction and activation of macrophages and their secretion products as cytokines and growth factors.

The Classic Model of Adhesion Formation: A Local Phenomenon

A trauma of the peritoneum, involving besides the mesothelial cells also the basal membrane and the subendothelial connective tissue, is followed by a local inflammatory reaction, exudation, and fibrin deposition (Fig. 2). This fibrin is normally

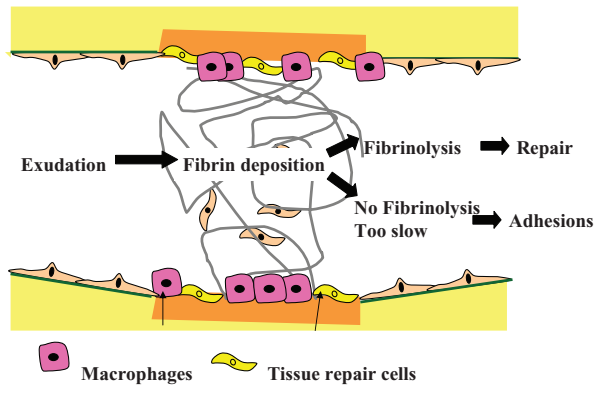

Figure 2 The classic model of adhesion formation as a local process with trauma, exudation and fibrin deposition, fibrinolysis, and rapid repair involving macrophages and tissue repair cells.

rapidly removed by fibrinolysis (40) while simultaneously the peritoneal repair process is started (41). Within hours of injury, the injured area is covered by what is believed macrophages and "tissue repair cells," which within three to four days differentiate into mesenchymal cells. Repair starts specifically from numerous small islands, and the repair of small and large areas therefore is similar. Given the concept of mesenchymal stem cells, the discussion about the exact nature of macrophages and tissue repair cells has acquired a new dimension, whereas the specific mechanism of repair starting from numerous small islands is easily understood (42). If the normal rapid repair of peritoneal lesions fails or when repair is delayed, other processes that were activated become dominant. Within four to six days, fibroblast proliferation invading the fibrin scaffold and angiogenesis starts, leading invariably to adhesion formation. The importance of the fibrin scaffold between two injured surfaces was elegantly demonstrated since separating these areas by Silastic membranes for up to 30 hours abolished adhesion formation (41). This type of experiments reinforced the belief that adhesion formation is a local process and that prevention should aim at separating the surfaces for at least two days. In addition, medical treatment given intravenously or intraperitoneally has been considered less important because this type of treatment would have difficulties reaching the injured zone because of local ischemia and it being shielded by the fibrin plug. The pathophysiology of this local process has been considered an inflammatory reaction, with players and mechanisms as fibrinolysis, plasmin activation, and PAIs, local macrophages and their secretion products and the overall oxygenation of the area or the absence thereof driving angiogenesis, fibroblast proliferation, and mesothelial repair. The focus on macrophages and tissue repair cells is changing rapidly given the actual concept to consider these stem cells.

Other arguments in favor of viewing adhesion formation as a local process are derived from the observations that some organs are more adhesiogenic than others and that this may be related to their fibrinolytic activity. A local process shielded from the rest of the peritoneal cavity seems also supported by the observation that normally peritoneal infection is kept localized by fibrin and adhesions. If not, a generalized peritonitis can become life-threatening.

Little is known about the mechanisms that determine whether adhesions will be velamentous, thick, and or vascularized and what factors determine innervations (43–45). Also adhesion remodeling is something that is poorly understood.

The Updated Model: The Peritoneal Cavity as a Cofactor

Studies published since mid-nineties have shown that the entire peritoneal cavity can be a cofactor in adhesion formation (7,8,22,23,46–60). Identified so far in laparoscopic rabbit and mouse models for adhesion formation are desiccation, hypoxia, reactive oxygen species (ROS), and manipulation (60), which increase adhesion formation at an injured area. Since CO_2 pneumoperitoneum–induced mesothelial hypoxia results in the entire exposed peritoneal area in retraction of mesothelial cells exposing directly the extracellular matrix (34–39), it is postulated that this results in the attraction into peritoneal fluid of substances of cellular elements and thus enhances adhesion formation and/or decrease repair, without causing adhesion formation outside the injured area. For hypoxia by CO_2 pneumoperitoneum, or for desiccation, one might argue that they also affect the injured site. The observation, however, of a similar dose-dependent effect following manipulation of the omentum and organs outside the injured area supports the concept that the entire peritoneal cavity can be a cofactor in adhesion formation (Fig. 3).

It seems logical to postulate that any trauma to the large and flat mesothelial cells will induce them to retract as a defense mechanism and that this effect is more pronounced when trauma is more severe. However, we do not know what the exact mechanisms are through which adhesion formation is further modulated. We only can speculate that macrophages and their secretion products, blood constituents, or other inflammatory products affect directly the repair process or the differentiation of stem cells at the injured area. Any postulated mechanism should explain that desiccation enhances

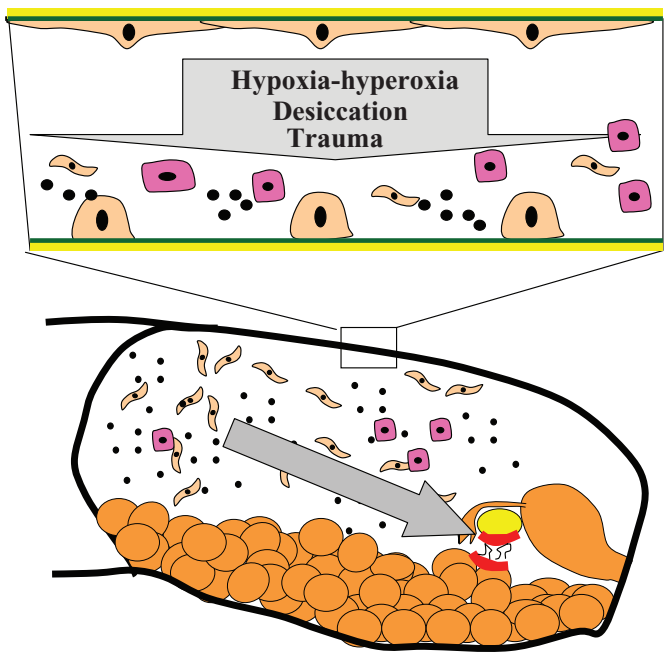

Figure 3 The updated model of adhesion formation. Flat mesothelial cells respond to trauma by retraction and bulging, exposing directly the extracellular matrix. The peritoneal fluid subsequently increases adhesion formation at the trauma site.

adhesion formation and that the effect is dose dependent. CO_2 pneumoperitoneum also enhances adhesion formation and the effect is pressure and duration dependent. The effect upon adhesions seems mediated through mesothelial hypoxia since the mesothelial layer stains hypoxic and since the increase in adhesions is prevented by the addition of 3% to 4% of oxygen (restoring the physiologic intraperitoneal partial oxygen pressure of 30–40 mm Hg) and is absent in mice partially deficient for hypoxia-inducible factor-1α and 2α (HIF1α and HIF2α) being the first to be activated by hypoxia. Similar effects are observed when partial oxygen pressures exceed 80 mm Hg, thus increasing ROS, and this effect can be prevented by ROS scavengers.

Pathophysiology of Adhesion Formation: Conclusions

The classic model, which views adhesion formation as a local phenomenon (Fig. 2), and the effect of the entire peritoneal cavity (Fig. 3) and its constituents should be considered as complementary. The importance of each effect might vary with the localization and the type of injury. Following severe traumas, large areas, e.g., the pelvic cavity, can become completely occluded by fibrinous adhesions and these areas probably escape from the influence of peritoneal fluid. In these circumstances, adhesion formation may follow mainly the classic model. For minor lesions, especially nonapposed lesions, such as those frequently occurring during fertility surgery, the effect of the peritoneal cavity probably is dominant.

Both models are also important for our understanding of adhesions prevention agents. A flotation agent will also dilute peritoneal fluid and any factor secreted locally by the denuded areas as well as will hamper the access of macrophages, which cannot swim. Barriers on the other hand might, in addition to keeping tissues separated, shield the injured area from the peritoneal fluid and its constituents, something that might be beneficial or detrimental according to circumstances.

To understand the role of the mesothelial cells in peritoneal repair, both models have to be considered simultaneously. Obviously, peritoneal repair and adhesion formation between injured areas is a local process. The repair cells, however, are at least partially derived from incorporation of free-floating mesothelial cells in the peritoneal fluid, which today could be considered partially differentiated stem or progenitor cells. Since repair can be accelerated and adhesion formation decreased, by intraperitoneal injection and transplantation of autologous mesothelial cells, any deleterious effect to the peritoneal cavity is bound to affect these free-floating cells. Today we can only speculate about endocrine or other factors affecting the function of these cells and even about the sheer number of cells available for repair. It is unclear whether, as a response to trauma of the peritoneal cavity by hypoxia or desiccation, the number of free-floating mesothelial cells/stem cells are expected to be increased by attraction or to be decreased because free-floating cells could attach to cover the denuded areas in between retracted mesothelial cells. The importance of mesothelial cell and their differentiation is also highlighted by the observation that the fibroblast cultured from adhesions are permanently differentiated from other mesothelial fibroblasts (61–63) and by the observation that recurrence rates after adhesiolysis are much higher than expected.

Clinically, some individuals form adhesions more easily after surgery than others—an observation supported by the fact that some mice strains form much more adhesions than others—while variability of adhesion formation is much lower in inbred strains (53). We also do not know why some adhesions are filmy and thin while other adhesions are dense; why some adhesions are vascular or avascular, or innervated or not.

PREVALENCE AND CLINICAL CONSEQUENCES OF POSTOPERATIVE ADHESION FORMATION

Following abdominal surgery, adhesions are formed in over 70% of women, and they have been considered as a cause of infertility, pain, and bowel obstructions (Fig. 4). The clinical importance of adhesion formation has been emphasized by the SCAR study (9–11) demonstrating in a 10-year follow-up of abdominal surgery in Scotland that the incidence of reoperation and of bowel obstruction kept rising almost linearly for a period of at least 10 years. Moreover, reinterventions occurred in some 30%, in many persons more than once, and at least 6% could be linked directly to adhesion formation. Repeat surgery was more difficult, more tedious, and associated with more complications because of adhesions. From these findings, models have been constructed, calculating cost of adhesions formation for society, and conversely the savings that could be realized by adhesion prevention assuming that reduction in adhesion formation could linearly be extrapolated to a reduction in pain, in infertility, and in repeat surgery or bowel obstructions.

The real clinical picture, however, is not so clear. The first confounding factor is quality of surgery, which is variable. Duration of surgery and complication rates decrease by training as demonstrated in a series of learning curves in both humans and animal models. Both the duration of endoscopic surgery and the extent of manipulation have been demonstrated to directly affect adhesion formation. It must be recognized that in contrast with medical therapy for which quality control is strictly organized, there is no quality control for surgery (12). Further, there are no data available permitting to judge the importance of adhesion formation for fertility, not even after fertility-promoting surgery. The results reported rather reflect centers of excellence and it is hard to judge whether differences in results are the consequence of techniques, indications, or surgeons. Finally, the introduction of laparoscopic surgery has probably decreased the overall quality of fertility surgery. Indeed, during the eighties fertility surgery was performed in specialized centers by surgeons highly trained in microsurgery, who had an important clinical interest in adhesion prevention and who had developed the concepts of gentle tissue handling and moistening. The introduction of endoscopic surgery, a surgical access route used by most general gynecologists, had as a consequence that generalists started performing fertility surgery, irrespective of training. That quality went down is difficult to prove given the absence of quality control in surgery, but the exponential rise in IVF cycles over the world might be due to some extent to the decrease in the training and hence to the use and to the quality of this type of surgery. If this is true, adhesion formation is a key factor.

That adhesions cause pain is widely believed based upon the observations that adhesions can be innervated (43,45) and that under local anesthesia, palpation of adhesions can cause pain (64,65). However, at present, we clearly cannot predict which adhesions cause pain or whether adhesiolysis would be beneficial. Given this variability in the relationship between pain and adhesions, and given the variable rate of adhesion reformation, it is not surprising that the results of adhesiolysis are still debated. Individual studies have reported pain reduction, but this could be due to placebo effect after surgery,

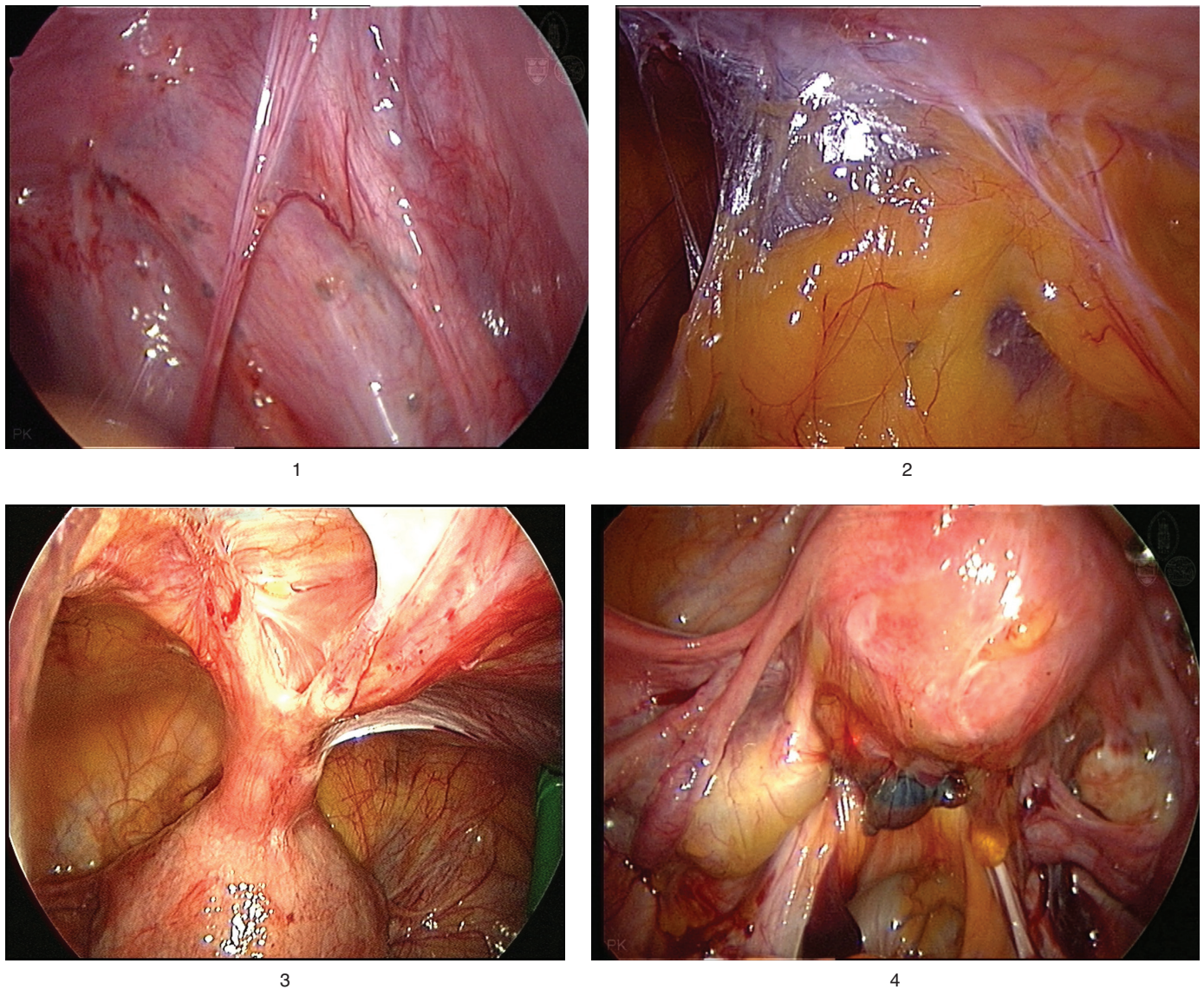

Figure 4 Adhesions vary from short but strong bands (**1**), causing eventually bowel obstruction, to filmy adhesions between omentum and the appendectomy scar (**2**) to dense vascularised adhesions between uterus and abdominal wall (**3**) to dense adhesions as seen in endometriosis (**4**).

whereas the only randomized control trials did not demonstrate a clear effect upon pain (66).

PREVENTION OF POSTOPERATIVE ADHESION FORMATION

Adhesion formation between opposing injured peritoneal surfaces are acknowledged to be different from adhesion reformation following lysis of adhesions and from *de novo* adhesion formation outside the areas of surgery. Since adhesion prevention has been investigated adequately only for the former, the following paragraphs will not discuss *de novo* adhesions and adhesion reformation.

Good Surgical Practice and Conditioning of the Peritoneal Cavity

Good surgical practice and gentle tissue handling have been introduced as an important tenet by the pioneers of microsurgery. This includes moistening of tissues by continuous irrigation, moistening of abdominal packs, glass or plastic rods for mobilization of tissues, and precise microinstruments. Reduction in adhesion formation was anticipated. However, it is only recently that the importance of prevention of desiccation and of gentle tissue handling have been proven, emphasizing how important and accurate clinical observation can be.

Key to good surgical practice today is whether the animal data can be extrapolated to humans. These data probably can be extrapolated because the effect of CO_2 pneumoperitoneum, the duration-dependent increased CO_2 resorption, observed in mice and in rabbits also occurs in women. Taking into account the findings in animal models, good surgical practice today should include the following. First, the insufflation gas should be conditioned in order to minimize hypoxia and desiccation; this requires humidification of the gas and the addition of 3% to 4% of oxygen to the CO_2. Moreover, cooling of the peritoneal cavity is important since it decreases both the effects of hypoxia and of desiccation, cells being more resistant to

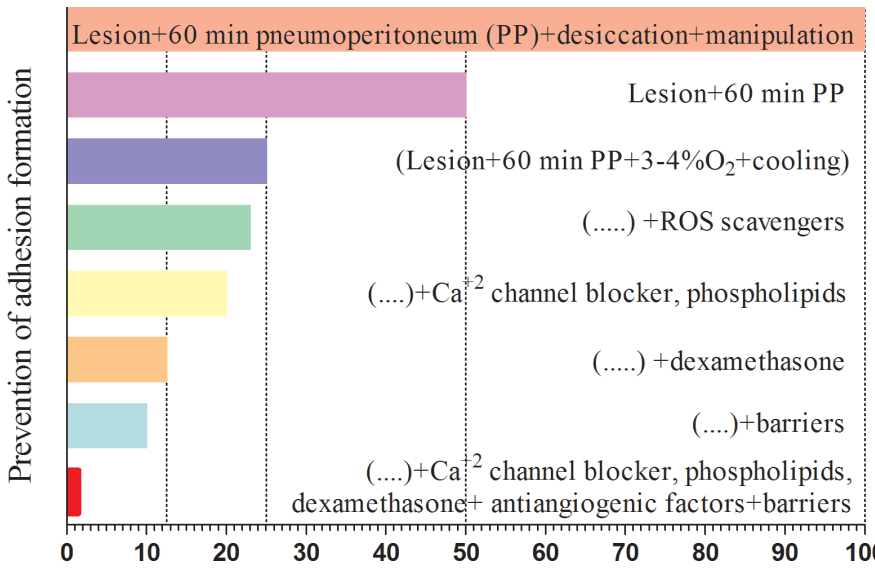

Figure 5 Prevention of adhesion formation in a laparoscopic mouse model. Minimizing mesothelial damage by preventing desiccation, gentle tissue handling, adding oxygen, and cooling decrease adhesion formation to some 25%. Adhesions decrease further by adding ROS scavengers, calcium channel blockers, phospholipids, or dexamethasone. In addition barrier gels can be used for over 90% reduction in adhesion formation. If in this model, calcium channel blockers, phospholipids, antiangiogenic monoclonal antibodies, and fibroblast manipulation would have additional effect, close to 100% adhesion reduction might be achieved.

metabolic damage at lower temperatures. Cooling of the peritoneal cavity makes it possible for the humidified and saturated insufflation gas to condense upon entrance to the pelvic cavity, thus preventing desiccation. Secondly, the duration of surgery should be kept to a minimum as well as the amount of bleeding and the extent of tissue manipulation. In summary, the surgeon should be experienced and well trained.

Observation of strict sterility remains mandatory to prevent any kind of infection. This simple statement should be balanced against the observation that it is difficult to completely disinfect the umbilicus and that each time the vagina is opened, at least some risk of infection occurs. This is even more likely with entry into the bowel. Good surgical practice therefore should begin by observing strict sterile conditions. This might sound obvious but it is not so evident, since in endoscopic surgery many surgeons no longer wear masks (endoscopic surgery being considered a semisterile intervention). Looking carefully at endoscopic interventions many minor mistakes are noticed if judged by the standards of open surgery. Whether extensive lavage following surgery might reduce adhesion formation or the risk of some minor infection is unknown. Following deep endometriosis surgery with full thickness resection and a bowel suture, extensive lavage with 8 L clearly decreased the postoperative inflammation as judged by CRP concentrations while preventing late bowel perforations (De Cicco C, unpublished observations). This has stimulated us to extend the use of extensive lavage to all surgical interventions with an increased risk of infection such as following hysterectomy or salpingostomy for hydrosalpinx. Interestingly, microsurgery also emphasized lavage for removing clots, foreign substances, and fibrin.

Taken together these measures of good surgical practice along with conditioning of the pneumoperitoneum, cooling and prevention of inflammation, should reduce adhesion formation by more than 60%.

Adhesion Prevention in Animal Models

A wide range of products have been shown to be effective in animal models. Efficacy of all products described so far has been extensively investigated in our laparoscopic mouse model. It should be realized that in this model all criteria of good surgical practice as described are fulfilled, with standardized lesions, controlled duration of surgery, strict control of temperature, and absence of desiccation (Fig. 5). It should also be realized that the laparoscopic mouse model is a model for three distinct pneumoperitoneum conditions: normoxia, hypoxia, and hyperoxia. The first model intends to minimize any peritoneal damage except for the lesions inflicted to induce adhesions. Thus, adhesions will form according to the classic model, with little or no effect of the peritoneal cavity. In this model, 4% of oxygen was added to the CO_2 pneumoperitoneum to prevent mesothelial hypoxia. The second model is the "hypoxia model" since adhesions are enhanced by CO_2 pneumoperitoneum–induced mesothelial hypoxia. In this model, pure CO_2 was used. In the third model, called hyperoxia model, 12% of oxygen was added to the CO_2 pneumoperitoneum, a concentration known to enhance adhesions probably by cell damage by ROS.

Dexamethasone decrease adhesions by some 30% in the hypoxia model (47), by 60% in the hyperoxia model (67), and, especially, by some 76% in the normoxia model when it is combined with low temperature (68). ROS scavengers decrease adhesions by 10% to 15% in both the hypoxia and hyperoxia models, an effect too small to be demonstrated in the normoxia model, with much less adhesions to start with. Calcium channel blockers decrease adhesion formation by some 35% of inhibition in both hypoxia (47) and hyperoxia models, and around 58% in the normoxia model when is combined with low temperature; recombinant plasminogen activator (rPA) decrease adhesion formation by 40% in the hypoxia (69) and normoxia models, whereas less inhibition, around 17%, was

observed in the hyperoxia model. Ringers lactate as a flotation agent is marginally but significantly effective (51). The effects of other flotation agents such as carboxymethylcellulose (CMC) and Hyskon are marginal (46) and surfactants such as phospholipids give some 35% of inhibition in the hypoxia and hyperoxia models and 58% in the normoxia model when it is combined with low temperature. Icodextrin (Adept, 4% α (1-4) glucose polymer) unfortunately could not be evaluated since it is degraded enzymatically in mice. Barriers such as Hyalobarrier gel, Spraygel, and Intercoat are highly effective in all models with a reduction of 58% to 90% in adhesion formation.

Prevention of angiogenesis also reduces adhesion formation, as demonstrated in PlGF knockout mice and by the administration of anti-VEGF and anti-PlGF monoclonal antibodies (55,56,61–63,70,71).

The transplantation of cultured mesothelial cells into the peritoneal cavity also is effective in decreasing adhesion formation (72,73) and in remodeling the area of mesothelial denudation. More recently, mesothelial cells were used as transplantable tissue-engineered artificial peritoneum and research is focusing on the use of mesothelial progenitor cells (74).

Adhesion Prevention in Humans

Adhesion prevention in humans has been limited to barriers and flotation agents with a reduction of adhesion formation that ranges, for all products, between 40% and 50%. Most important is that for none of these products efficacy has been proven for endpoints that really matter, i.e., pain, infertility, bowel obstruction, or reoperation rate. We should also realize that large randomized controlled trials were needed because of the high intraindividual variability and that in these trials the surgical interventions were limited to rather simple and straightforward interventions as cystectomy and myomectomy. In addition, these trials have been performed during interventions performed by laparotomy or by laparoscopy under conditions of CO_2 pneumoperitoneum–enhanced adhesion formation and slight desiccation. It, therefore, is still unclear to what extend the available results of efficacy can be extrapolated to more severe or other types of surgery, and whether in the human the effect will be additive to good surgical practice and conditioning of the peritoneal cavity (46).

Sheet barriers such as Seprafilm (hyaluronic acid–carboxymethylcellulose) (75–77), Interceed (oxidized regenerated cellulose), (78,79) and Gore-Tex (expanded polytetrafluoroethylene) (80) are proven effective but did not become very popular for various reasons. Seprafilm is difficult to use during laparoscopy, Interceed requires the removal of any remaining bleeding to be efficacious, whereas Gore-Tex, being nondegradable, must be removed from the applied site during a second surgery.

Since Intergel (0.5% ferric hyaluronate gel) has been withdrawn from the market, only Hyalobarrier gel [auto-crosslinked hyaluronic acid gel (81)], Spraygel (polyethylenglycol), and Intercoat/Oxiplex (82,83) remain available for clinical use. Overall efficacy appears to be similar for all three products. A comparison between these three gels can unfortunately not be made since comparative trials do not exist. Also the strength of the available evidence varies and a Cochrane review of hyaluronic acid and Spraygel concluded that only for hyaluronic acid the evidence was solid (84).

While in humans the efficacy of Ringers lactate as a flotation agent has not been proven, Adept (Icodextrin) (85–87), a macromolecular sugar with a higher retention time in the peritoneal cavity, was expected and shown to be efficacious in adhesion reduction. A major advantage is the safety and absence of side effects, which were well established since this has been extensively used for peritoneal dialysis. The strength of the available evidence demonstrating efficacy was in a Cochrane review not considered very solid (84).

Strong arguments can be found in the literature to use LHRH agonist prior to surgery as adhesion prevention (88), but specific clinical trials are lacking.

DISCUSSION AND A LOOK INTO THE FUTURE

The concept of mesothelial cells as stem cells, which can be transplanted to peritoneal trauma areas to modulate repair and decrease adhesion formation in animal models, is actually stimulating research aimed at collecting large amounts of autologous mesothelial stem cells and at manipulating them in culture prior to transplantation. Simultaneously, the addition to the peritoneal fluid of factors known to stimulate resident mesothelial proliferation or mobilization or differentiation are investigated in order to decrease adhesion formation (89). Both the activation and multiplication of mesothelial cells is expected to be developed into new strategies to reduce postoperative adhesion formation (24,90,91). Also, the potential of using mesothelial stem cells derived from muscle is actively been investigated (92).

Immense progress has been made over the last 15 years in our understanding of the pathophysiology of adhesion formation and the mechanisms involved. Besides the traditional concept viewing adhesion formation as a local inflammation with fibrin deposition and removal, the peritoneal cavity has been demonstrated to have an important role. Hence good surgical practice, gentle tissue handling, prevention of desiccation, hypoxia and ROS production, and conditioning of the peritoneal cavity by cooling have become the first key aspects in prevention of adhesion formation. Since the mechanisms by which the peritoneal cavity influences adhesion formation remains unexplored we may reasonably expect that in the near future we will be able to decrease adhesion formation even further.

Inhibition of fibroblast proliferation obviously is an objective in adhesion prevention. The use of dexamethasone to reduce adhesion formation has been around since a long time but the efficacy has been debated and questioned. In our laparoscopic mouse model especially under conditions of minimal trauma to the peritoneal cavity the effectiveness was very pronounced. This was surprising, since other anti-inflammatory agents such as COX1 and COX2 inhibitors were not effective. Therefore, dexamethasone is suggested to be effective, and that not because it is an anti-inflammatory agent but because it inhibits mesothelial proliferation. This is also consistent with the observations that dexamethasone reduces cell proliferation, collagen deposition, and lung fibrosis (93). The hormonal factors modulating fibroblast proliferation are being extensively investigated and hepatocyte-derived growth factor (HGF) has been demonstrated to prevent peritoneal fibrosis. (94,95). That HGF is also effective in reducing adhesion formation was demonstrated by "painting" with adenovirus containing the HGF gene directly onto surface of the injured area (96).

Since we understand that during adhesion formation different mechanisms are sequentially involved, adhesion prevention strategies should aim no longer at only one

mechanism but consider sequentially all different mechanisms. By doing so, we can decrease adhesion formation by more than 90% in animal models. Prevention of adhesions will start with good surgical practice, conditioning of the peritoneal cavity through cooling, and prevention of desiccation and of hypoxia by adding 3% to 4% of oxygen. This will reduce adhesion formation by over 50%. If all the last strategies are associated with products as ROS scavengers and dexamethasone, adhesion formation in mice drops by an additional 30% this means to an 80% to 85% of total adhesion reduction. If at the end of surgery, barriers are added, which by themselves are more than 50% effective, the cumulative adhesion formation reduction has been proven today to be more than 90%. Since the mechanisms through which the following products decrease adhesion formation are different from those listed before, we may expect that the effects will be additive. Indeed, effectivity between 30% and 40% was demonstrated for phospholipids and calcium channel blockers, whereas drugs preventing angiogenesis, by blocking PlGF of VEGF, are even more effective. This has not been demonstrated yet since in models in which adhesion formation is already reduced by more than 90%, it becomes statistically difficult to prove additional effects. In conclusion, it seems reasonable to expect virtually adhesion-free surgery in not too distant future.

SUMMARY

We have been aware for a long time that adhesions occur almost systematically in at least over 80% of women undergoing abdominal surgery. The widely held belief has been that adhesion formation increases with the severity of surgery and with infection but that this could largely be prevented by good quality surgery. Thus, postoperative adhesion formation has for many years been emotionally ignored by the "good surgeons." Only in the last decade, we have become aware of the clinical importance of adhesion formation, mainly though the SCAR studies, which have clearly demonstrated that the incidences of bowel obstruction and of reoperation due to postoperative adhesions keep increasing linearly for at least 10 years and are much higher than anticipated. That postoperative adhesions can cause infertility and pain is well known, although quantitative data are missing.

Adhesions formation between traumatized areas has traditionally been considered as a local process, i.e., an inflammatory reaction, exudation, and fibrin deposition followed by fibrinolysis and mesothelial repair. If the repair process is slowed down by infection, or very severe surgical trauma, locally insufficient blood supply, or foreign bodies such as sutures, a process of fibroblast proliferation together with angiogenesis starts and adhesions are formed. Key in this concept is that the fibrin is used as a scaffold for this process and that without prior fibrinous attachment between surfaces, adhesions do not occur. Over the last decade, awareness has grown that secretions and/or cells from the entire peritoneal cavity strongly influence this local phenomenon. The factors identified so far are desiccation, mesothelial hypoxia as it occurs during CO_2 pneumoperitoneum, ROS, which occurs during open surgery, and mesothelial trauma as a result of grasping and manipulation of intraperitoneal organs. If judged from animal models, this peritoneal effect is quantitatively much more important than the local phenomenon.

Prevention of adhesion formation therefore traditionally has focused upon good surgical practices and upon barriers or flotation agents or barriers preventing fibrinous attachments between injured surfaces. Flotation agents as Ringers lactate are marginally effective, whereas Adept has claimed 40% to 50% effectiveness explained by an increased retention time. Mechanical barriers produced as sheets (Seprafilm, Interceed, or Gore-Tex) and gels (Spraygel, Hyalobarrier gel, Intercoat) have also shown some 40% to 50% effectiveness albeit for specific interventions performed by recognized good surgeons only. Most importantly this is a highly variable efficacy and it remains unknown whether this variability in adhesions and in prevention is patient or intervention or surgeon dependent. In any case, for none of these products efficacy has been demonstrated for the clinically important endpoints such as pain, infertility, or reoperation rate.

The concept emphasizing the importance of the peritoneal cavity has opened new approaches to prevention. Gentle tissue handling is getting a new dimension: during surgery the peritoneal cavity should be conditioned by preventing hypoxia (adding 3% to 4% of oxygen to the pneumoperitoneum), by preventing desiccation (using humidified gas), and by cooling, when using laparoscopy as surgical access. In animal models these factors in combination are effective in reducing adhesions way over 80%. If used together with products such as dexamethasone and barriers, an overall efficacy over 95% maybe obtained.

We are at the beginning of understanding the mechanisms by which the peritoneal cavity affects adhesion formation. Although today the focus is on prevention of deleterious factors, we must also focus on increasing favorable factors and recognize the importance of peritoneal stem cells in the repair process.

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